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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/844,353	RUVKUN ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *5-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 April 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner. See PTO 948.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1, 8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 03/24/03 has been acknowledged.

Election/Restrictions

Applicant's election without traverse of Group I (*Claims 1-4, wherein the elected subject matter is a nematode or an isolated nematode cell*) in Paper No. 7 is acknowledged.

Claims 1-11 are pending.

Claims 5-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7.

Claims 1-4 are examined in this office action.

► Applicants are advised to follow Amendment Practice under revised 37 CFR §1.121 (*http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm*). Each amendment document that includes a change to an existing claim, or submission of a new claim, **must include a complete listing of all claims** in the application. After each claim number, the status must be indicated in a parenthetical expression, and the text of each claim under examination (with markings to show current changes) must be presented. The listing will serve to replace all prior versions of the claims in the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a method of identifying a modulatory compound that is capable of decreasing the expression or activity of daf-16 gene in a nematode or an isolated nematode cell. The scope of invention as claimed encompasses identification of modulatory compound that decreases the expression or activity of daf-16 gene (obtained from any and all organisms) in any and all nematodes. At best the specification disclosed *C. elegans daf-16* gene (spec. page 38, Fig-13 and 14) and its function in *C. elegans* worm. Besides *C. elegans daf-16* gene the instant specification fails to disclose *daf-16 gene* obtained from any other organisms.

Applicant is referred to the Interim guidelines on *Written Description* published December 21, 1999 in the Federal Register, Vol. 64, No. 244, pp. 71427-71440. The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In the instant case the specification only teaches *C. elegans daf-16* gene but fails to disclose any other *daf-16 gene or nematode daf-16* that has the functional property of *C. elegans daf-16* polypeptide explicitly or implicitly. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USP2d 1481 at 1483. In Fiddes, claims directed to a mammalian FGF's were found to be unpatentable due to lack of written description for that broad class wherein the specification provided only the bovine sequence.

The possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v.*

WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).* In the instant case the daf-16 gene (as claimed) has been defined only by a statement of a function that broadly encompasses the modulation of daf-16 expression or activity by a compound, which conveyed no distinguishing information about the identity of the claimed genetic sequence, such as its relevant structural or physical characteristics.

In addition, mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976). According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus

because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

2. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a compound that decreases the expression or activity of *C. elegans daf-16* gene in a *C. elegans* or an isolated *C. elegans* cell, does not reasonably provide enablement for the method as claimed that requires the decrease in expression or activity of *daf-16* (obtained from any and all organisms) in any and all nematodes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature Of Invention:

The invention relates to a method of identifying a compound that decreases the expression or activity of *daf-16* gene in a nematode or an isolated nematode cell, wherein the compound is a candidate compound for ameliorating or delaying an impaired glucose tolerance condition, atherosclerosis or obesity.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of invention as claimed encompasses identification of a modulatory compound that decreases the expression or activity of daf-16 gene (obtained from any and all organisms) in any and all nematodes. At best the specification disclosed *C. elegans daf-16* gene (spec. page 38, Fig-13 and 14). Besides *C. elegans daf-16* gene the instant specification fails to disclose *daf-16*

gene obtained from any other organisms. In addition the specification fails to disclose the making of any transgenic nematode that encodes an exogenous daf-16 transgene obtained from any and all organism.

State Of Art And Predictability:

The state of art at the time of filing teaches that the genetic interaction among various *daf* genes and/or gene products is complex and is only well understood in *C.elegans* (Larsan et al, Genetics 139:1567-83, 1995). The scope of instant invention encompasses the making and use of any and all genetically engineered nematodes encoding any *daf-16 like* gene obtained from any animals selected from the entire animal kingdom. Art a the time of filing teaches that human FKHR and AFX are the probable human orthologs of *C. elegans daf-16* gene but with sequence similarly of only 65% and 62% respectively in fork head DNA binding domain (Ogg et al, Nature 389:994-999, 1997, page 995, col.2 para.4). It is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976. Therefore considering the limited sequence similarly and lack of single working example in the specification it is highly

unpredictable that human FKHR or AFX would substitute the function of endogenous *daf-16* in any and all nematodes or isolated cells thereof.

In addition making of a transgenic nematode that encodes an exogenous *daf-16* transgene is considered unpredictable too, since the phenotypic characteristic of an animal is determined by a complex interaction of genetics and environment. (Wood. Comp. Med. 50(1): 12-15, 2000, see page12). The phenotype examined in a transgenic and/or knock out model is influenced by genetic background, which is the collection of all genes present in an organism that influence a trait or traits. The genes may be part of same biochemical or signaling pathway or of an opposing pathway or may appear unrelated to the gene being studied. Furthermore, allelic variations and the interactions between the allelic variants also influence a particular phenotype. These epigenetic effects can dramatically alter the observed phenotype and therefore can influence or later the conclusions drawn form the transgenic or knockout models (Sigmund, Arterioscler. Throm. Vasc. Biol.20:1425-1429, 2000, see page 1425). In instant case, the genetic interaction among various DAF genes and/or gene products is complex and is only well studied in C.elegans (Larsan et al). Furthermore, nematodes are one of the most widespread and abundant groups of animal and there are approximately 12,000 species of nematodes (Ville at al, General Zoology, Sixth Edition, Saunders College Publication, 1984, see pages 509-516). The instant specification even fails to provide any evidence that *daf-16* gene and function has been conserved through out phylum nematoda. Therefore is it unpredictable that any nematode ortholog of *C. elegans daf-16* gene would substitute the functional activity of *C. elegans daf-16 gene* even in *C. elegans*. Therefore, Applicant has not presented enablement commensurate in scope with the claims

Quantity Of Experimentation Required:

In instant case screening candidate compounds (which ameliorate or delay an impaired glucose tolerance condition, atherosclerosis or obesity) that decrease the expression or activity of any *daf-16 gene* (obtained from any and all organisms) in any and all nematodes or an isolated cell thereof is not considered routine in the art and without sufficient guidance to specific nematode genetic environment the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the unpredictability in the art and the limited guidance provided in the specification as filed one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. The undue experimentation required would include making and testing any and all nematodes or genetically engineered nematode cells encoding any *daf-16* like genes obtained from any and all organisms.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Gottlieb et al (Genetics 137:107-120, 1994).

The cited art teaches a method for identifying a compound that modulates the expression and activity of *C. elegans daf-16 gene in C. elegans* (page 118, fig-4). The cited art teaches isolation of new alleles of *daf-16* alleles and construction of worms encoding *daf-16* wild-type or mutated *daf-16* transgenes (page 108, col1, para.2; pages 109-110). The cited art further teaches that to monitor the role of *daf-16* in dauer formation the worms were exposed to high pheromone/low food conditions in liquid media (page 113, col2, para.4). The cited art teaches the treatment of 10,0000 L1 worms with 5ul of pheremone (*a candidate compound*) at 25°C for 50-100 hours. The cited art further teaches dauer formation assay in liquid and on plates (page 109, col.1 para 4-5). The cited art further teaches using high pheromone/low food conditions there is greater than 95% dauer formation in wild-type worms. The cited art teaches that *daf-16* is required both to initiate dauer formation as well as to maintain the dauer-differentiated state (page 114. col.1 para.1; page 115, fig-3). The cited art also confirm these results using plates containing high level of phaeromone and little food (page 114, col1. para.2). The cited art teaches that pheromone down regulates both *daf-2 and daf-13* pathway, and other major daf-c pathways (page 114 col.1 para.3). The cited art further teaches that *daf-16* functions down stream of both *daf-2 and daf-23* (page 116, col.1 para.2). Based upon the data, the cited art presented a model to explain the function of *daf-2, daf-23* and *daf-16* in the regulation of dauer formation and continuous development (page 118, fig-4). The cited art teaches that up-regulation of *daf-2 and daf-23* down-regulate the *daf-16* expression. The high pheromone treatment down-regulates the daf-2 and daf-23 and up-regulates the *daf-16* expression (page 119, col.2, page 118, fig-4).

Therefore the cited art clearly teaches a method that can identify a compound that is capable of decreasing the expression or activity of *daf-16* gene (see page 118, fig-4). Furthermore, the dauer-larvae has been characterized by a thin body (non-obese) relative to normal L3 worms (page 111, fig- 2, col.1 lines 12-15). Thus given the broadest reasonable interpretation the cited art clearly anticipate the invention as claimed.

Claim Objections

4. Claim 1 is objected to because of the following informalities: The instant claim is replete with grammatical and idiomatic errors. In line 6, insertion of -- wherein -- before " a decrease in daf-16 expression" and in line 8 replacing "identifying" with -- identifies -- before "a modulatory" has been suggested. Appropriate correction is required.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
PATENT EXAMINER

SUMESH KAUSHAL
PATENT EXAMINER